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PHYSICOCHEMICAL STUDY OF DRUG BINARY SYTEMS

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PHYSICOCHEMICAL STUDY OF DRUG BINARY SYSTEMS

[Fiziko-khimicheskoe issledovanie binarnikh sistem lekarstvennykh veshchestv]

SUMMARY

Physicochemical analytical methods were used to exa... following model system: amidopyrine-phenacetin, ane... nicotinamide, levomycetin-urea. All the three syste... ascertained to be of eutectic type. The interaction o... system components was analyzed on the kinetic of their t... to hydrochloric acid solution having pH 1.2 from me... mixtures and fusion cakes. The liquescency diagram and th... bility diagram were constructed for the systems. The ... rison of the diagrams revealed their relationship. The tr... rate for components to solution was found to be the m... for eutectic compositions. The experimental findings ... applied to predict the release rate for components ... drug compositions, to modify their composition, to im... their process more rationally.

A key point in the bioavailability of poorly and sparingly soluble drugs for internal use is the rate of passage of the active principle into solution, since absorption takes place only in dissolved state [5]. An increase of the rate of solution by mechanical micronization of substances cannot always be achieved. This is due to the occurrence of processes of agglomeration and aggregation of crystals and to degradation of the wettability of a superfine powder.

Current research gives results of the search for the optimum dispersity and also an evaluation of the mutual effect of system components on their dissolving, which was done by the techniques and methods of physicochemical analysis.

Studies were carried out on model binary systems of biologically active substances. Preparations of amidopyrine, phenacetin, anesthesine, nicotinamide, levomycetin and urea meeting the specifications of normative technical documentation were used as starting components. The substances were additionally purified by repeated recrystallization from water-alcohol solutions until they gave constant melting points. The degree of purity was determined by X-ray phase analysis (XPA), differential thermal analysis (DTA) and spectrophotometric analysis.

XPA was carried out on a DRON-3.0 apparatus with CuK_α radiation, quartz monochromator, and internal standard of semiconductor purity metallic germanium. The X-ray patterns were interpreted by using ASTM card files. All peaks on the X-ray patterns of

phenacetin, anesthesine, levomycetin and urea were identified with respect to the basic substance. Several unidentified peaks with intensities less than 5% were observed for the samples of amidopyrine and nicotinamide, which points to the existence of trace impurities that are not eliminated by the purification methods that were used.

The melting points and thermal stability of the preparations were determined by DTA on an apparatus consisting of a shaft type heating oven, a heating-cooling programmer, an amplifier to amplify the EMS of the differential thermocouple, and a two-point automatic potentiometer of type KSP. Aluminum crucibles were used, the heating-cooling rate was 10°C/min, and the sample weight was about 0.1 g.

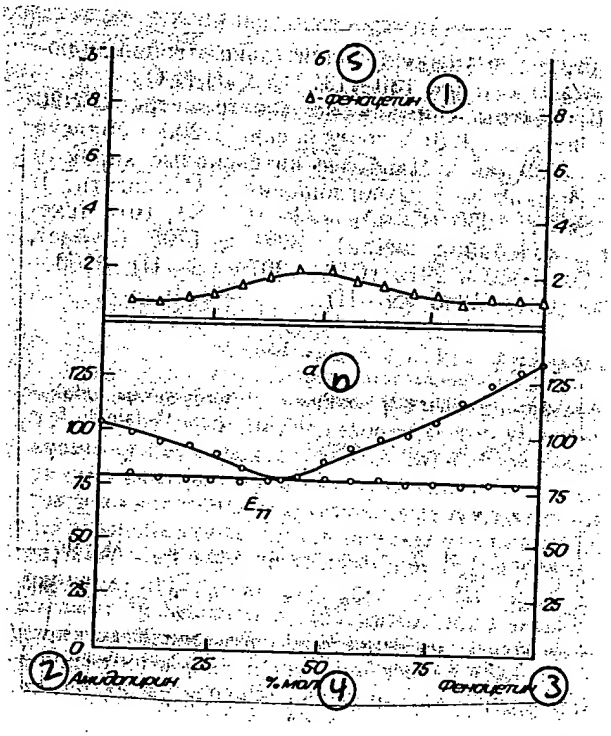

Figure 1. Diagrams of melting (a) and of composition vs. rate of solution (b) of amidopyridine-phenacetin system.

Here and in Figures 2 and 3 the composition in mol% is plotted on the x axis and the temperature in °C on the y axis.

Key: 1 Δ-phenacetin
2 Amidopyridine

3 Phenacetin
4 mol%
5 b
6 a

Thermal stability was controlled from the melting points of the substances in a mode of threefold heating-cooling cycles. The tests showed that the melting points of amidopyrine, phenacetin, anesthesine, nicotinamide, levomycetin and urea are stable and are respectively 107, 135, 90, 130, 149 and 128°C. These temperatures do not contradict the literature data, within the error limits of the experiments [3,7].

The absence of decomposition products after melting was demonstrated in parallel by XPA.

Three binary systems combining amidopyrine and phenacetin, anesthesine and nicotinamide, and levomycetin and urea, were formed from the samples, with the ratios of the components being varied every 5%. The geometric interpretation of the data from the thermal experiments showed the type of physicochemical status of the systems (Figures 1-3). All three systems are of eutectic type, and the compositions and melting points of the eutectics are given in Table 1. The liquidus points of the phase diagrams were additionally refined by visual-polythermal analysis (VPA). X-ray phase analyses of samples of the melts over the entire ranges of the systems showed absence of new phases in them, which supports the given type of phase diagram.

The rate of solution of the components from mechanical mixtures and melts into a solution of hydrochloric acid with pH 1.2 in a volume of 500 mL was determined for all of these system compositions. Kinetic experiments were conducted on a setup with a rotary stirrer, with the medium being stirred at 100 rpm. The tested compositions were tabletted by direct pressing under a pressure of 5 mPa, with tablets weighing 0.3 g and 12 mm in diameter. Fractions in the 200 μm size range were chosen for molding. The molten samples were cooled in a glass mortar immersed in ice. The tablets were secured at the bottom of a thermostatted vessel. Samples were collected at intervals of 2, 4, 6, 8, 10, 15, 20, 25 and 30 min, and their volumes were compensated with pure solvent. The ingredients were determined quantitatively by spectrophotometry. The concentrations were calculated by Firordt's method (except for the levomycetin-urea system) using the following equations [4,6]:

$$C_1 = \frac{E_2^{\lambda 2} \cdot D^{\lambda 1} - E_2^{\lambda 1} \cdot D^{\lambda 2}}{(E_2^{\lambda 1} \cdot E_1^{\lambda 2} - E_1^{\lambda 2} \cdot E_2^{\lambda 1}) \cdot l},$$

$$C_2 = \frac{E_1^{\lambda 1} \cdot D^{\lambda 2} - E_1^{\lambda 2} \cdot D^{\lambda 1}}{(E_2^{\lambda 1} \cdot E_1^{\lambda 2} - E_1^{\lambda 2} \cdot E_2^{\lambda 1}) \cdot l},$$

where $E_1^{\lambda 1}, E_1^{\lambda 2}$ and $E_2^{\lambda 1}, E_2^{\lambda 2}$

are the specific absorptions of the components C_1 and C_2 at wavelengths λ_1 and λ_2, $D^{\lambda 1}$ and $D^{\lambda 2}$ are the optical densities at wavelengths λ_1 and λ_2, l is the thickness of the cuvette.

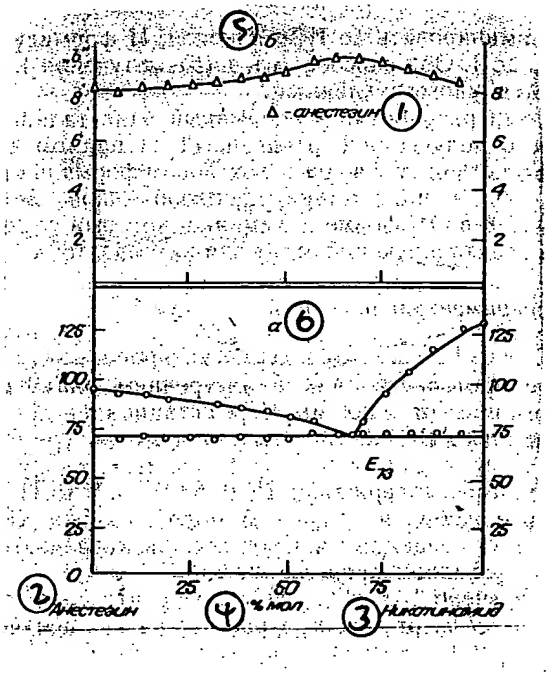

Figure 2. Diagrams of melting (a) and of composition vs. rate of solution (b) of anesthesine-nicotinamide system.

Key: 1 Δ-anesthesine
2 Anesthesine
3 Nicotinamide

4 mol%
5 b
6 a

For the levomycetin-urea system only the concentration of the antibiotic was determined, since urea does not have light absorption peaks in this wavelength range.

The reproducibility of the technique was verified beforehand in six repetitions for the amidopyridine-phenacetin system. The relative error of the measurements for a 95% confidence interval was ±1.37%.

Kinetic curves were plotted for all of the compositions of the systems from the results of determining the degree of passage of the components into solution from the samples. The profiles of the release curves of the components from each binary system had the same shape. Moreover, the profiles of solution both of the pure substances and the corresponding samples of melts and mechanical mixtures had analogous profiles.

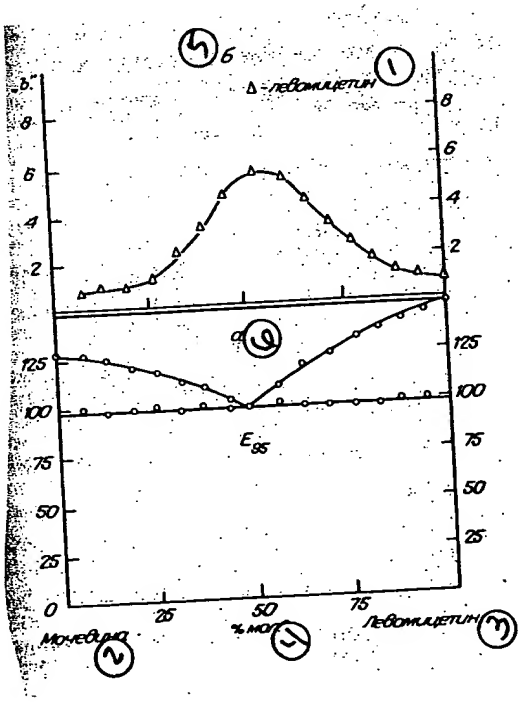

Figure 3. Diagram of melting (a) and of composition vs. rate of solution (b) of levomycetin-urea system.

Key: 1 Δ-levomycetin
2 Urea
3 Levomycetin
4 mol%
5 b
6 a

The method of converting the segment of the curves before reaching the plateau by using a least squares treatment was used to determine their intensity of slope, which quantitatively was characterized by the annular coefficient "b" in the equation: $y = bx + a$, where y is the concentration of substance passing into solution (μg/mL) and x is time (min). Proof of a linear relationship and an index of the rigidity of the linear connection between the values of the concentration of the components in the solution and time of solution is the value of the correlation coefficient "r," which in all cases exceeded a value of 0.95.

Diagrams of composition versus rate of solution were plotted from the experimental data for the tested systems (see Figures 1-3) and these diagrams graphically reflect the mutual effect of the components on the kinetics of solution. In a combined analysis of the diagrams of melting and the rate of solution it is seen that it is specifically the eutectic compositions that are characterized by the maximum increase of the rate of passage into solution of the components that form the system when compared to the analogous parameters for the starting substances.

The effects of an increase of the rates of release of poorly soluble substances from eutectic compositions are given in Table 2.

The observed effects, in the absence of interaction of the components of the mixture, can evidently be attributed to a decrease of the degree of crystallinity and the solubilizing effect of the substances. As is known, when the components of a eutectic mixture cool they crystallize at the same time, with maximum degree of dispersity of the solid phases. In turn, an increase of specific surface serves as a factor for increasing the rate of solution. The factor of an absence or a significant reduction of aggregation and agglomeration of the particles of eutectic mixtures plays a not unimportant role. The magnitude of the rate increase effects is also dependent on the difference of solubilities of the starting components of the systems. The effect of the solubilizing action can quantitatively be characterized by indices defined as the ratio of the angular coefficients of the starting components of the mixtures. For the amidopyrine-phenacetin model the index is equal to 30, while for the anesthesine-nicotinamide system it is 10. Tests have

demonstrated the very high effect of an increase of the rate of solution for the levomycetin-urea pair (see Table 2) using a hydrophilic carrier capable of wetting the surface of the crystals.

Table 1. Compositions and melting points of eutectics

Система (1)	Состав эвтектики, % мол. (% мас.) (2)	Температура, °С (3)
Амидопирин — фенацетин (4)	65 (71) 35 (29)	77
Анестезин — никотинамид (5)	33 (40) 67 (60)	73
Левомицетин — мочевина (6)	50 (84) 50 (16)	95

Key: 1 System
2 Composition of eutectic, mol% (wt%)
3 Temperature, °C
4 Amidopyridine-phenacetin
5 Anesthesine-nicotinamide
6 Levomycetin-urea

The identity of the composition-rate of solution diagrams to the diagrams of melting also confirms the results of the DTA, VPA and XPA studies indicating absence of interactions of the components of the system. Still another argument in favor of the reliability of these data is the identity of the UV spectra and the specific indices of absorption of the solutions both of the physical mixtures and their tabletted samples, and also the melts of a number of the system compositions.

Thus, the research results demonstrated the soundness of using the DTA, VPA and XPA methods to describe the properties of the systems overall as sufficiently precise methods for a rapid assessment of the compatibility of ingredients in combined drug forms, of their stability under "temperature stresses," which reflected the advantage of a system analysis over preparative chemical methods.

The described chemical tests of the systems using the techniques and methods of physicochemical analysis unambiguously excluded the probability of the development of effects of mutual interaction in the case of tabletting in a rigid press mold, of unforeseen changes in the composition of the preparations owing to the release of heat in the pressing process [1].

Table 2. Rate of solution of sparingly soluble components from eutectic mixtures and a melt of the systems

(1) Система	(2) Труднорастворимый компонент	Скорость растворения индивидуального (3) вещества, «b»	Скорость растворения из эвтектического состава, «b» (4)		Прирост скорости растворения (5)	
			смеси (6)	плава (7)	смеси (6)	плава (7)
(8) Амидопирин — фенацетин	Фенацетин (11)	1,1	1,3	1,7	1,2	1,5
(9) Анестезин — никотинамид	Анестезин (12)	8,2	8,5	9,0	1,0	1,1
(10) Левомицетин — мочевина	Левомицетин (13)	1,2	4,3	5,5	3,3	5,0

Key:
1 System
2 Sparingly soluble component
3 Rate of solution of individual substance "b"
4 Rate of solution from eutectic composition, "b"
5 Increase of rate of solution
6 Of mixture
7 Of melt
8 Amidopyridine-phenacetin
9 Anesthesine-nicotinamide
10 Levomycetin-urea
11 Phenacetin
12 Anesthesine
13 Levomycetin

The possibility of using melting as a method of preparing the tested drug mixtures for tabletting by producing finely divided mixtures of them was established. Melts of eutectic composition, along with this, support stabilization of the disperse state of the phases, the homogeneity of the mixture of components and an increase of the accuracy of dispensing as a result of more efficient mixing of the ingredients in molten state.

The experimental data can also be of practical interest for rational industrial solution to the problem [2] of safe grinding of pharmaceutical substances that tend toward ignition in a mode of mechanical dispersion (anesthesine, levomycetin).

The tests had as a goal the demonstration of the multi-informational nature of using physicochemical analysis to solve a number of biopharmaceutical problems of designing multicomponent solid drug forms. The steps in the work can represent a program of seeking compositions for medical purposes with specific properties on the basis of an analysis of the diagrams of state of multicomponent systems with proof of the coordinated change of the properties of the equilibrium systems (and in this case solubility) as a function of their composition.

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